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STERILIZING IMMUNITY AGAINST HEPATITIS C VIRUS IS SUBTYPE SPECIFIC, IS APPARENTLY NOT MEDIATED BY NEUTRALIZING ANTIBODIES, BUT IS CORRELATED WITH ANAMNESTIC CELLULAR IMMUNE RESPONSES. Jens Bukh, National Institutes of Health, Bethesda, MD; Robert Thimme, Scripps Research Inst, La Jolla, CA; William Satterfield, Univ of Texas M D Anderson Cancer Ctr, Bastrop, TX; Xavier Forns, National Institutes of Health, Bethesda, MD; Kyong-Mi Chang, Scripps Research Inst, La Jolla, CA; Masayuki Yanagi, Suzanne U Emerson, National Institutes of Health, Bethesda, MD; Francis V Chisari, Scripps Research Inst, La Jolla, CA; Robert H Purcell, National Institutes of Health, Bethesda, MD

Although it is well established that hepatitis C virus (HCV) infection is resolved in a subset of cases, the critical components of immunity to HCV have not been determined. Furthermore, it was previously reported that HCV infection does not confer protection against challenge with quasispecies even of the same strain. In the present study, a chimpanzee that was convalescent from a monoclonal HCV infection (genotype 1a) was repeatedly challenged with HCV. In the original infection, viremia persisted for 23 weeks, then cleared for more than 6 months. A peripheral HCV-specific CD4+ T cell response was detected during the acute phase and anti-HCV (second generation ELISA) was detected from week 15. Three subsequent challenges with homologous monoclonal virus [3 to 320 50% chimpanzee infectious doses (CID_{50})] resulted in transient viremia (2 weeks duration) or absence of viremia. Analysis of the virus genomic sequence (entire open reading frame) recovered from the chimpanzee following the first re-challenge demonstrated that it did not represent an immune escape variant. An anamnestic humoral response and a peripheral CD4+ T cell response occurred following each challenge. The chimpanzee was next challenged with the homologous polyclonal virus pool known to contain an infectious quasispecies with significant heterogeneity within the envelope proteins, in particular within the hypervariable region 1. Interestingly, it did not have viremia following each of three consecutive challenges with 6+ CID_{50}, 6+ CID_{50}, and 6+0 CID_{50}, respectively, of this polyclonal virus pool. Thus, this chimpanzee had developed sterilizing immunity against the homologous HCV strain. After each challenge we observed an anamnestic CD4+ T cell response. The chimpanzee developed a low level of antibodies to the hypervariable region 1 but not to other epitopes of E2 after the first challenge with 6+ CID_{50}. This sterilizing immunity to HCV was not due to a high titer of neutralizing antibodies. We attempted to neutralize HCV in vitro with "hyperimmune" serum obtained from the chimpanzee after the third challenge with polyclonal HCV: residual infectivity was tested by inoculating the neutralization mixture into a naive chimpanzee, which became infected. Following a subsequent challenge with 100 CID of a heterologous strain (genotype 1b) the "immune" chimpanzee developed transient viremia (weeks 1-12); a polyclonal virus population was recovered from the chimpanzee. A peripheral CD4+ T cell response was continuously detectable after the challenge and viral clearance was temporally associated with an intrahepatic CD4+ T cell response. Furthermore, the chimpanzee was not infected following subsequent repeated challenge with 100 CID, or with 1000 CID of this 1b strain. A similar virological and immunological phenomenon was observed following subsequent consecutive challenges with a polyclonal genotype 2a strain. Thus, immunity to HCV appeared to be subtype specific. A second chimpanzee with acute resolving monoclonal HCV infection is currently being re-challenged in a similar fashion. Our results have important implications for the prospects of developing broadly reactive HCV vaccines.

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LONG TERM RESULTS OF PATIENTS UNDERGOING LIVER TRANSPLANTATION FOR PRIMARY BILIARY CIRRHOSIS AT A SINGLE CENTER. Silvania P Cauduro, Russell H Wiesner, David J Brandhagen, Michael R Charlton, Ruud A Krom, Mayo Clinic, Rochester, MN

Primary biliary cirrhosis (PBC) is an autoimmune liver disease of unknown etiology, which follows a slowly progressive course to liver failure. Liver transplantation is the only established treatment for patients with advanced PBC. AIM: To analyze the outcome of liver transplantation for PBC at a single institution. METHODS: We analyzed 155 consecutive PBC patients (134 female, 21 male) undergoing liver transplantation who received a total of 176 allografts. Mean age at time of transplantation was 52 years. Patients were divided into two groups: those grafted between 1985 and 1992 (n=77) and those grafted between 1993 and 2000 (n=78). The analysis was done with data

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